them, inundating and destroying tissue, we would assume that more changes occur in vessels than meet the eye, also that, although vessels in the irradiated central nervous system appear morphologically intact, they can be nonetheless functionally defective."

Chambers claimed in 1940 that he saw a cell coat with the dissecting microscope which he assumed served as a cell cement. His observations were largely ignored at the time. More than a decade later, Wislocki (1951) visualized a coating using Periodic Acid Schiff (PAS) staining of stratified squamous epithelial cells and lateral surfaces of intestinal epithelium, areas previously believed to be uncoated. Indirect evidence of an extraneous adhesive cell coat was provided by Moscona (1952) who showed that cells lost their adhesiveness after being trypsinized. Rambourg, et al. (1967) in their review reported over fifty cell types in the rat as having stainable cell surfaces as seen with PAS staining. They also found that all of the cell surfaces stained using Mowry's colloidal iron (1963), a stain specific for acidic carbohydrate stains devised for the electron microscope; e.g., periodic acid with aldehydes and periodic acid-chromic acid-silver methanamine. Golgi saccules and inner surfaces of cytoplasmic vesicles were stained as well as cell membranes. They also stained cell surfaces for electron microscopic study with phosphotungstic acid.

Cervos-Navarro (1964) studied the brain cortex from an irradiated rabbit (1500-2500 rads Co-60 source) 6 and 12 months after exposure using the electron microscope, and noted damage to the capillary endothelial cells and the capillary basement membrane. Kristensson et al. (1967) studied the human spinal cord exposed to an estimated 5100R of X-irradiation. They noted a thickening of the walls of capillaries, arterioles and arteries under the light microscope. Dilated capillaries and flattened endothelial cells were also seen. Strel'Tsova, et al., (1968) observed changes in the kidneys of dogs exposed to neutron irradiation. They concluded that the radiation injury of the vascular system in the kidney resulted in the observed pathology. Maisin (1970) observed the ultrastructural changes in the lungs of mice exposed to whole-chest X-irradiation (2000 rads), over a period of 15 months. In the early phase of radiation damage (few hours to one month), edema was found in the interstitium, and clusters of platelets were found opposed to the capillary endothelium. Endothelial cells of the small capillaries showed the most intensive early damage. Permeability of capillaries to horseradish peroxidase was increased and some capillary edema was noted. Eight to fifteen months after exposure (delayed response), Maisin reported that the basal membrane of the capillaries was often very thick and edematous. Maisin concluded that functional changes in the capillary permeability occur very soon after irradiation.

Philpott, et al., (1973) have also observed this mucopolysaccharide (MPS) coating on endothelial cells (Fig. 1,2) in many different tissues (heart, lung, kidney, brain etc.) taken from young rats (one month, 120 gm) fixed with Ruthenium Red following Luft's technique (1971). In addition, it was observed that young rats subjected to 2400 rads of whole- body X-irradiation and sacrificed 24 and 48 hours later were essentially devoid of the MPS coating when examined with Luft's technique (Fig. 3). Marcum and co-workers (1986) demonstrated anticoagulative properties on the surface of aortic endothelial cells. They used cloned bovine aortic endothelial cells to synthesize anticoagulantly active heparan sulfate proteoglycans. Their binding studies using 125I-labeled antithrombin demonstrated that these proteoglycans are located on the surface of the cloned bovine aortic endothelial cells.

It seems quite plausible that the early disappearance of the MPS coating observed by Philpott et al., (1973,1974b) could be intimately related to the change in capillary permeability noted by so many observers of radiation damage to the capillary systems in a variety of tissues. In addition, Matsumura, et al. (1966) observed a 20% decrease in viscosity in a buffered solution of hyaluronic acid (an AMPS found in bacteria and animals) exposed to 2000 rads of X- irradiation, thus indicating depolymerization.

Polysaccharides, in general, represent ubiquitous macromolecules which are located throughout the body and play a role in health and disease. One such compound is heparin, an anticoagulant which is located in the mast cells around blood vessels and very similar in structure to the coating material. It is not unreasonable to suppose that the acid MPS coating on the lumen also functions as an anticoagulant. It's disappearance might explain Maisin's (1970) observation of clusters of platelets oppossed to the capilary endothelium. Cartilage contains another polysaccharide, chondroitin sulfate, while heart valves contain both

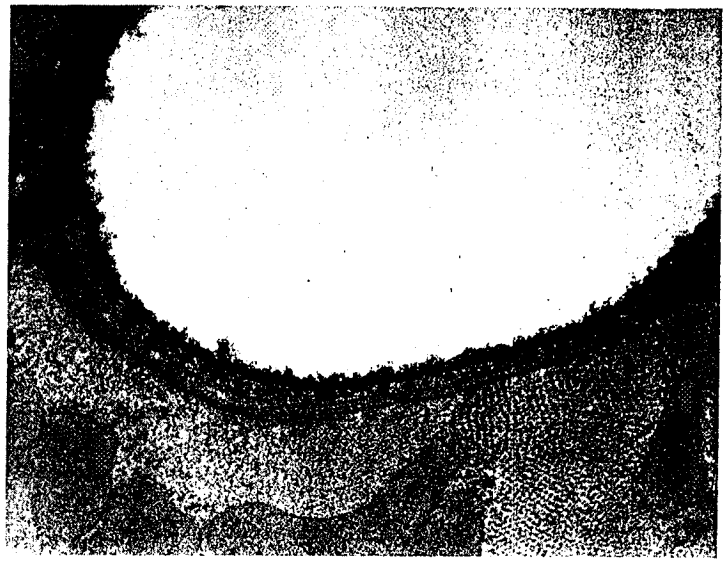

Figure 1. Normal Mouse Heart Capillary Stained with Ruthenium Red (RR). Note the Dark RR Material Lining the Lumen. 13,000X.

chondroitin sulfate A and B, plus hyaluronic acid. Cornea contains keratosulfate. Normal human plasma contains AMPS (Bassiouni 1955), but AMPS from the blood of patients with rheumatic fever or rheumatoid arthritis have anticoagulant activity not found in normals. Clinical use of MPS may have consequences. Bauer (1983) tested three MPS used to treat rheumatology. They found, Arteparon, to have anticoagulant properties and indicated attention should be paid to its use. Kirk and Dyerby (1957) isolated MPS containing mainly chondroitin sulfate A and B. The average yield from subjects under age 59 was 4.8 mg/g of wet tissue while a decrease of one half to 2.4 mg/g occurred in subjects 60-70 years old. Acidic MPS, which does not originate from the urinary tract or the prostate gland, has been

Figure 2. Normal Rat Lung Showing the Filamentous Nature of the RR Stained AMPS. 15,000X.

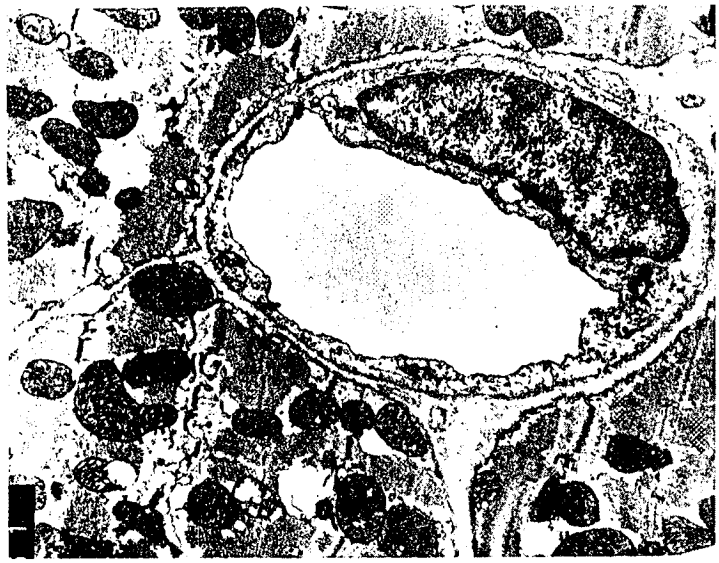

Figure 3. Rat Heart 48 Hours after 400 Rads of X-rays. RR Treated. Note Absence of Any AMPS Coating. 10,000X.

isolated from normal human urine. This AMPS is strongly metachromatic with toluidine blue and is hydrolyzed by testicular hyaluronidase. Electrophoresis of normal urine separated out three AMPS, and all three had some anticoagulant activity of the heparin type (Heremans, et al. 1959).

Hyaluronic acid, possibly the most studied MPS, shares many properties with the other MPS and forms part of the ground substance or matrix surrounding the cells. One of its suggested roles is to bind water in the interstitial spaces and to hold cells together in a jelly-like matrix (Meyer 1947) and another to resist compression and provide lubrication. The long polysaccharide molecule zig-zags back and forth, forming a loose but tangled "ball-of-string" network. It has been suggested as a role in restriction of movement of viruses and selective permeability of large molecules. Hyaluronic acid at a concentration of only 0.1% already forms a continuous meshwork of chains. Laurent (1977) has measured a two-fold increase in osmotic pressure over that of albumin in only a 1% solution of hyaluronic acid. This suggests a role in osmotic pressure regulation and is of obvious interest in capillary studies.

The cationic dyes, colloidal iron (Mowry 1963), thorium (Rambourg 1967), and Ruthenium Red (RR), (Luft 1966,1971) have been employed to visualize the cell coating and results had indicated the presence of acidic groups. Using these dyes plus Alcian Blue mixed with glutaraldehyde, Behnke (1968) demonstrated a MPS coating on red blood cells and platelets. His work with thorotrast indicated that this coat was on the order of 130 angstroms thick. He used trypsin digestion and showed that this treatment removed RR stained material, but colloidal iron and thorotrast showed binding to the cell surface. Luft's technique (1966) using RR has been the most widely used, yielding a dense coating easily visible in the electron microscope.

The properties of MPS, e.g., anticoagulant, osmotic pressure regulator, lubricant, mechanical barrier, etc., suggested several important roles for this structure along the lumen of blood vessels (Philpott 1973). It is hypothesized that reduction in the amount of coating, or its total removal, might very well cause osmotic pressure changes which in turn would alter capillary permeability. The network of intermeshed molecular strands could selectively restrict passage of macromolecules, a function which would also cease with MPS coat removal. Further roles played by the MPS coating the blood vessels may be the binding of water and

anti-shock. In addition, this MPS coat could play a role in the laminar flow observed between blood cells and the capillary wall.

Studies have been carried out to test the effect of various stressors on the blood vessel lining. Aging may be one of them. Strokes are, in general, a disease of the elderly. To shed some possible light on this problem, young and old rats were examined for MPS coating on the vessels of the brain and heart (Philpott 1973). The MPS coating was thinner and spotty in the old animals. Endotoxin also removes the MPS coat An injection of 10 or 20 mg/Kg of E coli endotoxin completely removes the coating in 24 hours in rats (Philpott 1974a). The breathing of 100% oxygen (Philpott 1973) and exposure to X-rays (Philpott 1974b) also removes this coating.

Interestingly, Davies and Gamble (1977) found that abdominal radiation of 500 to 1000 rads increased the permeability of the intestinal vasculature 24 hours after exposure. Willoughby (1960) found the same result in his radiation studies. Therefore, if radiation decreases the MPS coating and at the same time increases permeability, a very good case for cause and effect exists. It seems that this blood vessel coating may play several key roles in the normal maintenance of function and permeability of the blood vessels.

In view of the fact that the blood vessel coating may play a role in altering coagulation, the reports of Skylab III and Salyut 4 (Kimsey 1977) are most interesting. There was a post-flight decrease of 20-30% in fibrinogen and a two-fold increase in fibrinogen split products in two of the Skylab III crewmen and results from Salyut-4, 2 and 7 days post-flight, showed an increase in the total coagulative activity of the blood as indicated by an increase in the heparin tolerance of the blood, by an increase (48-69%) in the fibrinolytic activity of the blood, and by an increase in recalcification. It was suggested that the increase in thrombogenic properties might be related to dehydration of the body and that the increase in fibrinolytic activity might be related to stress effects. Hypercoagulability could be a problem, especially if crew members are drawn from older age groups where strokes are more common.

The duration of space flights is increasing and there is serious talk about a mission to Mars. The MPS coating of cells and especially blood vessels appears to be susceptible to conditions of space flight. By visualizing and measuring the MPS coating on the blood vessels, its role in normal animals and in those exposed to simulated and/or spaceflight conditions can be elucidated. Immobilization, radiation, altered G levels and endotoxins appear to affect the coating. Combinations of these stresses should also be studied to help quantitate the tissue response. The coating also appears to play a role in relation to capillary permeability and alterations in coagulation time.

Hypokinesia studies have investigated changes in general MPS metabolism and production, but have not covered the effects on the MPS coating of the blood vessels. There is a lack of information concerning this coating in relation to spaceflight problems.

METHODS

Six C-57 black mice were used for each radiation response study and six more were used as controls. Tissue staining of the MPS utilized Luft's method (1966). Six 120 gm rats were used to test coagulation times in each category of 1) controls, 2) endotoxin injection and 3) 400 and 800 rads of X-irradiation. Coagulation times were determined 10 and 24 hours after each treatment.

Disappearance of the MPS after X-irradiation was plotted after exposing heart tissue to 10, 40, 50, 100, 200, 400, 500, 1000, 1500, 2000 and 4000 rads of whole body irradiation. One hundred capillaries were chosen at random for each tissue and graded for the presence of the lumenal MPS coating after 24 and 48 hours.

Animals were irradiated in head only and chest only p=09 areas by X-rays and Neon particles to see if the removal of the MPS would be restricted to only these areas. Irradiated and non-irradiated areas were then selected for examination to test the theory that RR could be used as a selective marker for radiation.

Tissues were fixed by perfusion using 7% glutaraldehyde. The tissue was then sliced at 200 microns on a Vibratome and immersed in RR osmium solution. The following day selected tissues were rinsed briefly with buffer, and processed by routine embedding procedures. The energy dispensive X-ray analyzer attachment on the electron microscope was used for Ruthenium identification in the sections.

Luminal coating material was removed, collected and identified by the following procedure. Six young control rats, 180-210 gms, were perfused, first with 5-10 ml of Ringers and then with Ringer's containing trypsin. The trypsin flush removed the coating and the perfusate containing the MPS coating was collected. The MPS was removed by trypsin dissolved in 0.001 M HCl, then it was added to 0.01 cadodylate buffer to give 0.1 mg/ml of trypsin. Supernatant was collected and spun down. Perfusate was preserved in 1/3 ethyl alcohol, 2/3 trypsin solution. The method is repeated without trypsin for control. Following the trypsin flush, the animal was perfused with glutaraldehyde and following embedding and sectioning, the vessels were checked for coating. Gas liquid chromatography (GLC) was used to identify the components.

Using six rats for each dose, in-vivo coagulation time studies were carried out by placing five half-hitch loops of thread over each isolated femoral vein exposed on the rat hind leg (leaving the same space between each loop). One pull on the thread simultaneously tied off four sections of blood vessel, Fig. 4. By cutting open the vessel sections at timed intervals, in-vivo coagulation time was established.

Two month, eight month and two year old rats were treated with 10 and 20 mg/Kg of E. Coli endotoxin I.P. Tissues were examined after 10 and 24 hours. Heart and skeletal muscle, lung, liver, kidney, spleen, brain, retina, trachea, intestine, salivary gland, adrenal gland, gingiva and carotid artery were prepared for examination of the lumenal coating. Rats were also kept in 100% oxygen and 1 atmosphere for 72 hours.

RESULTS AND DISCUSSION

The eight month old rats proved the most resistant to the endotoxin treatment. This probably reflects the period when they are physiologically the strongest. Ten and twenty four hours of treatment resulted in increased loss of the MPS and increased damage to the capillaries and basement membrane. In general, the MPS loss preceded the cellular damage. The endotoxin affects the MPS luminal coating in a progressive manner in all of the tissues examined. While the lumen of the younger control rats had a continuous coating of the MPS, the two year old controls showed irregular aggregation of the MPS and general loss of thickness. Consequently, the two year old controls were not considered the best choice for general studies.

Reference to Table 1, shows the average reduction of in-vivo coagulation times after both endotoxin and irradiation. Since these treatments remove MPS, this indicates the MPS is at least partly responsible for anti-coagulative properties within blood vessels. GLC analysis was done (by Dr. M. Mathews, U. Chicago) for sugars identified manose, glactose,

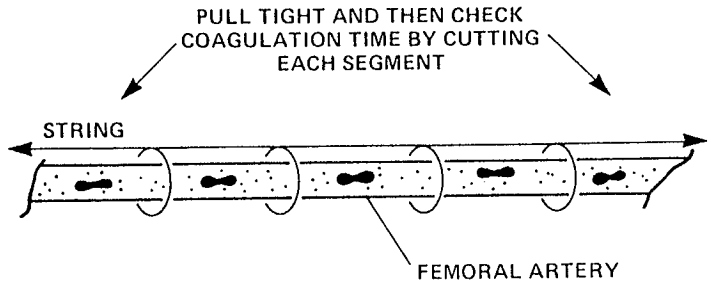

Figure 4. Schematic of in-situ Method Used to Determine Coagulation Times after X-irradiation of the Rat.

Table 1. Graph Showing the Loss of the AMPS after 24 and 48 Hours. The 2000 Rad Exposure is Not Shown as the AMPS is Essentially Removed.

Average Coagulation Time

Controls	E. Coli Endotoxin	X-irradiation
27 secs	10 mg/Kg; 10 hrs=20 secs	400rads; 10 hrs 17 secs
	10 mg/Kg; 24 hrs=15 secs	400rads; 24 hrs 15 secs
	20 mg/Kg; 10 hrs=20 secs	800rads; 10 hrs 18 secs
	20 mg/Kg; 24 hrs=20 secs	800rads; 24 hrs 16 secs

Table 2. Results of Gas Liquid Chromatography Analysis for Carbohydrate Components (mg) in Normal and Tadiation Exposed Rats.

	CONTROL mg	RADIATED 800 rads mg
MANNOSE	1.90	3.0
GLACTOSE	1.80	4.4
GLUCOSAMINE	2.52	3.6
NEURAMINIC ACID	3.08	6.5

glucosamine and N-acetylneurominc acid. Reference to Table 2, shows the amount found in controls as compared to animals exposed to 800 rads of X- rays four hours after irradiation.

The MPS interposes itself between the endothelium of the blood vessel walls and the blood elements. As such, any transcapillary exchange must take place through this layer. There are several possibilities for its function. The layer consists of long chain molecules which reduces friction when an object passes over a surface. A more important feature may be the resemblance of the MPS structure to heparin. The calcium binding of heparin confers anti-coagulant properties and the MPS also has calcium binding properties due to their sulfate and carboxyl groups. Ofosu, et. al. (1987) increased the sulfation of heparin sulfate and dermatan sulfate and found increasing the sulfation increased the anticoagulant activity. Thus the presence of the MPS would confer an important property to the blood vessels. Also, any MPS sloughed off from the lumen would be carried in the blood stream, its presence possibility decreasing the rate of coagulation. Disappearance of the MPS could have serious consequences. Since this coating also decreases with age, it may be associated with the increase of strokes in older people.

The susceptibility of the MPS to radiation has implications for the amount which is safe to absorb at any one time. More studies should be done on the recovery rate of the MPS coating after the various environmental insults.

The MPS coating appears quite sensitive to radiation. Reference to the graph (Fig. 5) shows that 85 to 90% of the coating is removed after 200 rads. The other tissues that had been prepared were briefly examined for their response and similar results were evident. This indicates the MPS is quite susceptible to depolymerization after irradiation.

Attempts to use the disappearance of the coating as a selective marker for the location of specific areas which had been irradiated failed. Both X-rays and Neon particle irradiation were used. Regardless of the area irradiated, all of the blood vessels in all the tissues examined had lost an equal amount of coating. Since the blood is circulating during the exposures and part of it is continuously passing through the area being irradiated, all of the blood is exposed. It is known that by-products, especially peroxides, are formed during irradiation and this may be the answer. Any by-products from the irradiation would have continuous access to the coating and could depolymerize the MPS. This result is strong

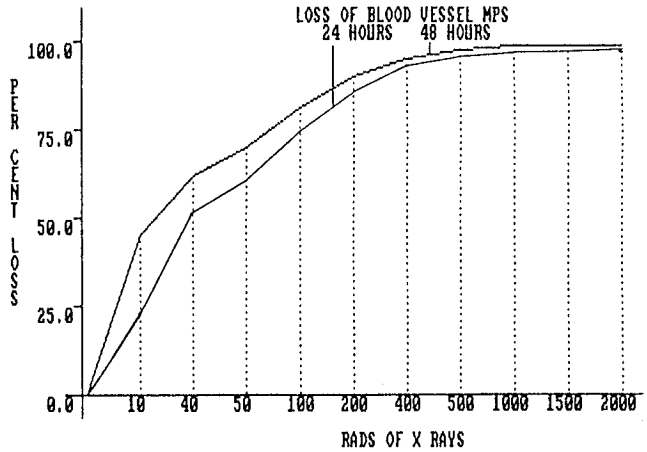

Figure 5. Graph showing the loss of the AMPS after 24 and 48 hours. The 4000 rad exposure is not shown as the AMPS is essentially removed.

evidence that deploymerization is an indirect effect of the radiation and may give clues to the real mechanism of its sensitivity.

Past investigations have visualized the coating, but techniques have not been quantitative or easily reproducible. The fluorescein method of Chernov (1965) measures capillary permeability, but it often only penetrates 3 or 4 cells deep. Ferritin labeling (Bruns and Palade 1968) does a better job at permeability and perhaps can be adapted to quantitating the lining layer and the change in permeability.

Environmental factors have been shown to effect MPS metabolism and production. A study by Mitsenko (1976) showed changes in MPS metabolism in individuals working in a hot environment. An accumulation of hexoses, seromucoids,ciruloplasmin in the blood and a decrease in fibrinolytic activity were seen. These changes affect components of the MPS lining, and the change in fibrinolytic activity may also show a correlation.

Fluid electrolyte levels and metabolism have been shown to be altered in space and during bed rest. Potapov (1977) suggested that investigation of MPS metabolism involved in binding and transport of fluids and inorganic ions should reveal new factors involved in impairing fluid and electrolyte metabolism during hypokinesia. Whether or not the MPS lining of blood vessels is involved should be investigated. His studies utilizing hypokinesia as a stressor reveals that phosphoric ethers of hexoses, which are immediate precursors of structural components of MPS, are used essentially to meet energy requirements of the organism and are therefore not available for the synthesis of hexosamines and hexuronic acid present in MPS.

SUMMARY

MPS layer exists which covers the luminal wall of blood vessels. This lining is thought to play a role in capillary permeability, coagulation, and lubrication of the vessel wall. It is also affected by radiation, infection, drugs, increased oxygen and age. All of these or combinations thereof can occur in space in addition to weightlessness. Reports from Salyut 4 disclosed an increase in total coagulative activity of the blood; reports from Skylab III also indicated coagulative changes. The mechanisms responsible for these changes remain unknown. Changes in MPS coating of blood vessels may play a significant role. It was suggested that the observed changes may be due to dehydration, but the role of MPS's was not known then. It appears that MPS may play quite a role in the reaction of the body to space flight.

A prediction model based on MPS coating changes could be developed to estimate the relevance for human long-term spaceflight exposure. Functional and structural relationships in the blood vessel wall and adjacent cellular structures should be delineated. In particular, clotting, fibrinogen leakage, alteration of pinocytotic vesicle size and number, and permeabililty need to be elucidated. Space flight experiments need to be planned in order to accurately determine the combined effects present in space.

Our early studies indicated that age reduces the coating thickness. An older group of astronauts may have a higher risk of thromboembolism in conjunction with thinning of the MPS layer if age is combined with radiation and/or infection, increasing the body's burden to the point of vascular malfunction. The susceptibility of the MPS to radiation has implications for the amount which is safe to absorb at any one time. Work should be done on the recovery rate of the MPS coating after the various environmental insults.

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